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(54) Title: USE OF SUBSTANCE P ANTAGONISTS FOR INFLUENCING THE CIRCADIAN TIMING SYSTEM

(57) Abstract: The present invention concerns the use of the compounds of formula (I) in the manufacture of medicaments useful for beneficially influencing the circadian timing system or enhancing the sleep efficiency of a mammal, suitably a human being. The compounds of formula (I) are described in full in WO 97/16440, WO 97/14324, WO 97/24350 and WO 97/24356.

USE OF SUBSTANCE P ANTAGONISTS FOR INFLUENCING THE CIRCADIAN TIMING SYSTEM

The present invention concerns the use of some particular substance P antagonists in the manufacture of medicaments useful for beneficially influencing the circadian timing system or enhancing the sleep efficiency of a mammal, suitably a human being.

There are a number of clinical and non-clinical applications for pharmaceutical agents, i.e. chronobiotics, that have the property for being able to shift mammalian, in particular human, circadian rhythms or to realign these rhythms to their appropriate position in the 24-hr environment. Such agents can be useful in the treatment of rhythm disturbances that have been associated with (a) sleep disorders of circadian nature of extrinsic type such as, for example, jet-lag or shift work sleep disorders, and of intrinsic type such as, for example, both phase advance and phase delay of normal sleep time, non-24hr sleep-wake syndrome, irregular sleep-wake pattern; (b) aging, psychiatric disorders, various forms of insomnia, Alzheimer's disease or other forms of dementia, depression, stress and anxiety.

Studies in animals, primarily rodents, have demonstrated that a variety of drugs and endogenous hormones/peptides can phase shift the mammalian circadian clock (Dawson and Armstrong, Pharmacol. Ther. Vol. 69, No. 1, pp. 15-36, 1996). Such substances are thought to influence the mammalian circadian clock by activating one or more of the input pathways to the central circadian pacemaker located in the hypothalamic suprachiasmatic nuclei (SCN), or by acting directly on the SCN neurons. Surprisingly, few attempts have been made to find drugs that can phase shift mammalian, in particular, human circadian rhythms.

The circumstances where the use of chronobiotics are most obvious are for shift work and jet-lag: two conditions which are not classified as a disease or a clinical problem. Although the market is enormous for drugs that could realign rhythms in humans engaged in shift work or rapid travel across time zones, it is only over the past decade that there has been a growing interest in the development of drugs that would "improve the quality of life" of individuals not suffering from any particular illness or disease. The use of chronobiotics have great potential not only for humans engaged in shift work and transmeridian travel, but also for humans who need to adjust the phase of their circadian clock to their desired work and social schedules. It is only in the last decade that rhythm disorders are recognized to be widespread in a number of disease states as well as in many elderly humans. For example many previously classified

"sleep disorders" may actually be a "circadian clock disorder", particularly in the elderly. Similarly, a hallmark of depression are the associated disruptions of normal sleep patterns, and for many depressed patients circadian disorders as well. Liver disease has recently been shown to have severe disruptive effects on sleep and circadian rhythmicity. Treating the circadian disorder in many clinical situations may have important therapeutic benefits for a variety of metabolic and mental disorders.

Literature shows that human circadian clock can be shifted by exposure to periods of bright light or dark, by short periods of exercise or by periods of sleep when the individual would normally be awake. (Buxton et al., Journal of Biological Rhythms 12(6):568-74, 1997 Dec.; Van Reeth O., Hormone Research. 49(3-4):158-62, 1998; Turek and Zee, Regulation of sleep and circadian rhythms, chpt. 5 & 8). These studies were extension of animal studies and demonstrate that human rhythms can be shifted in a similar manner as animals in response to different non-pharmacological agents. However, only two substances, melatonin and the benzodiazepine, triazolam, have been tested for their human phase shifting effects, and as in animals, both substances can induce phase shifts in human rhythms (Redfern P.H., Drugs 43 (2):146-153, 1992).

Although only triazolam (Copinschi et al., Sleep. 13(3):232-44, 1990 June) and melatonin (Sack R.L. et al., DN&P9(6), July 1996) have been demonstrated to be a true chronobiotic in humans (i.e. where one observes a clear shift in human rhythms in response to drug treatment), it has been shown, mainly from studies in depressed patients, that a number of pharmacological agents can have effects on the circadian clock (Klemfuss H., Pharmacol. Ther. 1992; 56(1):53-78; Healy and Waterhouse, Pharmac. Ther. Vol. 65. pp. 241-263, 1995; Duncan, Pharmacol. Ther. Vol. 71, No. 3, pp. 253-312, 1996). Similarly, drugs which are known to have antidepressant effects, including lithium and 5-HT related drugs, are also known to have chronobiotic effects in rodents (Mullins et al., Neuropsychopharmacology 1999-Vol. 21, No. 3).

A number of reports suggest that substance P plays a role in the overall circadian organization in mammals. Substance P is found in amacrine and ganglion cells of the retina (Brecha et al., Nature 327, 155-158, 1987; Li et al., Vis. Neurosci. 16, 475-481, 1999), the retino-hypothalamic axons projecting to the SCN (Takatsuji et al., Brain Res. 698, 53-61, 1995; Hartwich et al., Cell Tissue Res. 277, 351-361, 1994), the SCN (Hartwich et al., Cell Tissue Res. 277, 351-361, 1994; Mikkelsen and Larsen, Histochemistry 100, 3-16, 1993; Otori et al., Brain Res. 619, 271-277, 1993) and the IGL (Hartwich et al., Cell Tissue Res. 277, 351-361,1994; Moore and Card, J. Comp. Neurol. 344, 403-430, 1994). Treatment with substance P in in vitro preparations can

phase shift the circadian rhythm of neuronal firing activity in the SCN at circadian times when light pulses induce phase shifts in the locomotor activity rhythm of animals housed in constant darkness (Shibata et al., Brain Res. 597, 257-263, 1992). Substance P also stimulates the firing rate and glucose uptake in SCN neurons (Piggins et al., Brain Res. Bull. 37, 475-479, 1995; Shibata et al., Brain Res. 597, 257-263, 1992; Shirakawa and Moore, Brain Res. 642, 213-220, 1994). Microinjections of substance P induce small phase-delays in the hamster activity rhythm only when delivered during the early subjective night (Piggins et al., Brain Res. Bull. 42, 451-455, 1997). Local injections of spantide, a non-specific substance P receptor antagonist, reduce the light-induced expression of Fos in the SCN (Abe et al., Brain Res. 708, 135-142, 1996). These observations have raised the hypothesis that substance P participates in the entraining effects of light on the circadian system (Shirakawa and Moore, Brain Res. 642, 213-220, 1994).

The tachykinin family of neuropeptides, including substance P, neurokinins (NK) A and B, bind to three specific receptors, designated as NK1, NK2 and NK3. The NK1 subtype receptor is notably expressed in the circadian timing system, including the retina, the SCN and the IGL (Casini et al., J. Comp. Neurol. 389, 496-507, 1997; Mick et al., C. R. Acad. Sci. [III] 318, 209-217, 1995; Takatsuji et al., Brain Res. 698, 53-61, 1995). This receptor subtype is thought to mediate the modulation of substance P in the photic regulation of the circadian timing system (Challet et al., Brain Res. 800, 32-39, 1998; Shirakawa and Moore, Brain Res. 642, 213-220, 1994; Takatsuji et al., Brain Res. 698, 53-61,1995).

It has now been found that the compounds of formula (I) which are defined hereinafter can be used for the preparation of a medicament useful for beneficially influencing the circadian timing system of a mammal, suitably a human being. Said compounds are substance P antagonists and their preparation is described in WO 97/16440, WO 97/14324, WO 97/24350 and WO 97/24356. Thus, a method for beneficially influencing the circadian timing system of a mammal, suitably a human being, comprising the administration of a compound of formula (I) is provided.

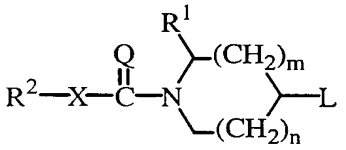
In particular, the present invention relates to the use of the compounds of formula (I) for the manufacture of a medicament useful for achieving a chronobiologic effect and alleviating circadian rhythm disorders in a mammal, suitably a human being. The present invention is also particularly related to the use of the compounds of formula (I) for the manufacture of a medicament useful for blocking or reducing the phase-shifting effects of light in a mammal, suitably a human being.

Thus, the present invention particularly concerns a method for achieving a chronobiologic effect and alleviating circadian rhythm disorders in a mammal, suitably a human being, comprising the administration of a compound of formula (I). The present invention is also particularly related to a method for blocking or reducing the phase-shifting effects of light in a mammal, suitably a human being, comprising the administration of a compound of formula (I).

The present invention also relates to the use of the compounds of formula (I) for the manufacture of a medicament useful for enhancing or improving sleep quality, particularly by increasing sleep efficiency and enlarging sleep maintenance, and for preventing and treating sleep disorders and sleep disturbances in a mammal, suitably a human being.

Thus, a method for enhancing or improving sleep quality, particularly by increasing sleep efficiency and enlarging sleep maintenance, and for preventing and treating sleep disorders and sleep disturbances in a mammal, suitably a human being, comprising the administration of a compound of formula (I) is also provided.

The compounds of formula (I) are defined as follows and are fully described in WO 97/16440, WO 97/14324, WO 97/24350 and WO 97/24356



(I)

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

n is 0, 1 or 2;

m is 1 or 2, provided that if m is 2, then n is 1;

=Q is =O or $=NR^3$;

X is a covalent bond or a bivalent radical of formula -O-, -S-, $-NR^3$-;

R^1 is Ar^1, Ar^1C_{1-6}alkyl or di(Ar^1)C_{1-6}alkyl, wherein each C_{1-6}alkyl group is optionally substituted with hydroxy, C_{1-4}alkyloxy, oxo or a ketalized oxo substituent of formula -O-CH_2-CH_2-O- or -O-CH_2-CH_2-CH_2-O-;

R^2 is Ar^2, Ar^2C_{1-6}alkyl, Het^1 or Het^1C_{1-6}alkyl;

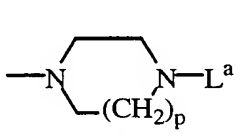
each R^3 independently is hydrogen or C_{1-6}alkyl;

each Ar^1 independently is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-4}alkyl, haloC_{1-4}alkyl, cyano, aminocarbonyl, C_{1-4}alkyloxy or haloC_{1-4}alkyloxy;

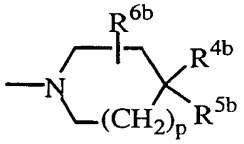
Ar^2 is naphtalenyl; phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from hydroxy, halo, cyano, nitro, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkyloxy, haloC_{1-4}alkyloxy, carboxyl, C_{1-4}alkyloxycarbonyl, aminocarbonyl and mono- or di(C_{1-4}alkyl)aminocarbonyl;

Het^1 is a monocyclic heterocycle selected from pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl and benzothienyl; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom by 1 or 2 substituents selected from halo, C_{1-4}alkyl or mono-, di- or tri(halo)methyl;

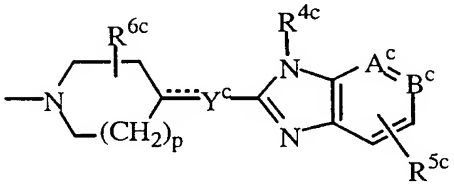
L is a radical of formula



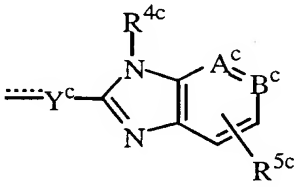
(A)



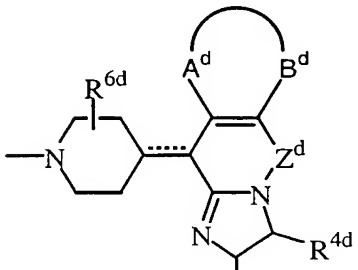
(B)



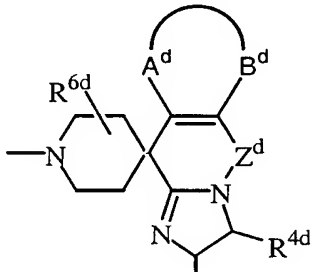
(C-1)



(C-2)



(D-1)

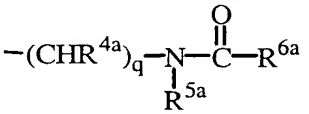


(D-2)

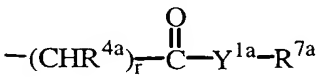
wherein

each p independently is 1 or 2;

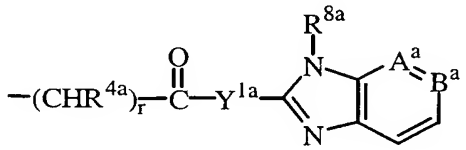
L^a is hydrogen; Ar^{3a}; C_{1-6}alkyl; C_{1-6}alkyl substituted with 1 or 2 substituents selected from hydroxy, C_{1-6}alkyloxy, Ar^{3a}, $Ar^{3a}C_{1-6}$alkyloxy and Het^{2a}; C_{3-6}alkenyl; $Ar^{3a}C_{3-6}$alkenyl; di(Ar^{3a})C_{3-6}alkenyl or a radical of formula



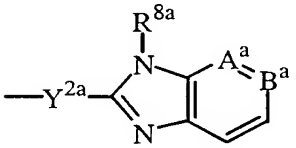
(A-a-1)



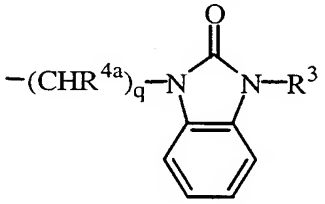
(A-a-2)



(A-a-3)



(A-a-4); or



(A-a-5)

wherein each q independently is 2, 3 or 4;

each r independently is 0, 1, 2, 3 or 4;

each Y^{1a} independently is a covalent bond, -O- or NR^3;

Y^{2a} is a covalent bond, C_{1-4}alkanediyl or -C_{1-4}alkylNR^3-;

each -A^a=B^a- independently is a bivalent radical of formula -CH=CH-, -N=CH- or -CH=N-;

each R^{4a} independently is hydrogen, C_{1-6}alkyl, Ar^2 or Ar^2C_{1-6}alkyl;

R^{5a} is hydrogen, C_{1-6}alkyl or Ar^{3a};

R^{6a} is C_{1-6}alkyl, Ar^{3a}, $Ar^{3a}C_{1-6}$alkyl, di(Ar^{3a})C_{1-6}alkyl, $Ar^{3a}C_{3-7}$cycloalkyl, or indolyl;

R^{7a} is Ar^{3a}; $Ar^{3a}C_{1-6}$alkyl; di(Ar^{3a})C_{1-6}alkyl; C_{1-6}alkyl; C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with Ar^{3a}; oxazolyl; oxazolyl substituted with halo or C_{1-6}alkyl; thiazolyl; thiazolyl substituted with halo or C_{1-6}alkyl; imidazolyl; imidazolyl substituted with Ar^{3a}, C_{1-6}alkyl, $Ar^{3a}C_{1-6}$alkyl or halo; indolinyl; indolinyl substituted with C_{1-4}alkyl; 2,3,4-trihydroquinolinyl; pyrrolidinyl or furanyl;

each R^{8a} independently is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl or a radical of formula

$-Alk^a-R^{11a}$ (A-b-1) or

$-Alk^a-Z^a-R^{12a}$ (A-b-2);

wherein Alk^a is C_{1-6}alkanediyl;

Z^a is a bivalent radical of formula -O-, -S- or $-NR^3-$;

R^{11a} is phenyl; phenyl substituted with 1 or 2 substituents selected from halo, C_{1-6}alkyl or C_{1-6}alkyloxy; furanyl; furanyl substituted with 1 or 2 substituents selected from C_{1-6}alkyl or hydroxy-C_{1-6}alkyl; thienyl; thienyl substituted with 1 or 2 substituents selected from halo or C_{1-6}alkyl; oxazolyl; oxazolyl substituted with 1 or 2 C_{1-6}alkyl substituents; thiazolyl; thiazolyl substituted with 1 or 2 C_{1-6}alkyl substituents; pyridinyl or pyridinyl substituted with 1 or 2 C_{1-6}alkyl substituents;

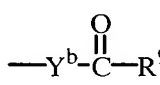
R^{12a} is C_{1-6}alkyl or C_{1-6}alkyl substituted with hydroxy, carboxyl or C_{1-6}alkyloxycarbonyl;

each Ar^{3a} independently is phenyl or phenyl substituted with 1, 2 or 3 substituents selected from halo, hydroxy, amino, nitro, aminocarbonyl, C_{1-6}alkyl, haloC_{1-6}alkyl or C_{1-6}alkyloxy;

each Het^{2a} independently is a heterocycle selected from 1,4-dihydro-5-oxo-tetrazol-1-yl, imidazo[1,2-a]pyridinyl, oxazolyl or imidazolyl; each of said heterocycles may be substituted with 1 or where possible 2 substituents selected from C_{1-4}alkyl and Ar^{3a};

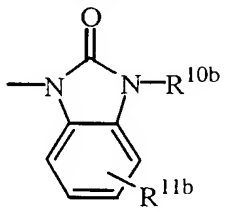
R^{4b} is hydrogen; C_{1-4}alkyl; C_{1-4}alkyloxyC_{1-4}alkyl; hydroxyC_{1-4}alkyl; carboxyl; C_{1-4}alkyloxycarbonyl or Ar^{3b};

R^{5b} is hydrogen; hydroxy; Ar^{3b}; $Ar^{3b}C_{1-6}$alkyloxy; di(Ar^{3b})C_{1-6}alkyloxy; $Ar^{3b}C_{1-6}$alkylthio; di(Ar^{3b})C_{1-6}alkylthio; $Ar^{3b}C_{1-6}$alkylsulfoxy; di(Ar^{3b})C_{1-6}alkylsulfoxy; $Ar^{3b}C_{1-6}$alkylsulfonyl; di(Ar^{3b})C_{1-6}alkylsulfonyl; $-NR^{7b}R^{8b}$; C_{1-6}alkyl substituted with $-NR^{7b}R^{8b}$; or a radical of formula



(B-a-1)

or



(B-a-2)

wherein R^{7b} is hydrogen; C_{1-6}alkyl; pyridinyl or Ar^{3b};

R^{8b} is hydrogen; C_{1-6}alkyl; $Ar^{3b}C_{1-6}$alkyl; di(Ar^{3b})C_{1-6}alkyl; imidazolyl substituted with Ar^{3b}, C_{1-6}alkyl or $Ar^{3b}C_{1-6}$alkyl; benzoxazolyl or benzothiazolyl;

R^{9b} is hydrogen; hydroxy; C_{1-6}alkyl; C_{1-6}alkyloxy; Ar^{3b}; $Ar^{3b}C_{1-6}$alkyl; di(Ar^{3b})-C_{1-6}alkyl; amino; mono- or di(C_{1-6}alkyl)amino; imidazolyl; imidazolyl substituted with Ar^{3b}, C_{1-6}alkyl or $Ar^{3b}C_{1-6}$alkyl; pyrrolidinyl; piperidinyl; homopiperidinyl; morpholinyl or thiomorpholinyl;

R^{10b} is hydrogen or C_{1-6}alkylcarbonyl;

R^{11b} is hydrogen; halo or mono-, di- or tri(halo)methyl;

Y^b is Y^{1b} or Y^{2b},

wherein Y^{1b} is a covalent bond; C_{1-6}alkanediyl; -NR^{7b}- or -C_{1-6}alkanediyl-NR^{7b}-; or

Y^{2b} is -O-, provided that R^{9b} is other than hydroxy or C_{1-6}alkyloxy;

R^{4b} and R^{5b} may also be taken together to form a bivalent radical of formula -O-CH_2-CH_2-O- or -C(=O)-NR^3-CH_2-NR^{7b}-;

R^{6b} is hydroxy; C_{1-6}alkyloxy; C_{1-6}alkyl or $Ar^{3b}C_{1-6}$alkyl;

Ar^{3b} is phenyl or phenyl substituted with 1, 2 or 3 substituents selected from halo, hydroxy, amino, nitro, aminocarbonyl, C_{1-6}alkyl, haloC_{1-6}alkyl or C_{1-6}alkyloxy;

$\overset{\cdots}{=}Y^c\overset{}{-}$ is a bivalent radical of formula -CH_2-, -CH(OH)-, -C(=O)-, -O-, -S-, -S(=O)-, -$S(=O)_2$-, -NR^3-, -CH_2-NR^3- or -C(=O)-NR^3-; or a trivalent radical of formula =CH-;

-A^c=B^c- is a bivalent radical of formula -CH=CH-, -N=CH- or -CH=N-;

R^{4c} is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl or a radical of formula

-Alk^c-R^{7c} (C-c-1) or

-Alk^c-Z^c-R^{8c} (C-c-2);

wherein Alk^c is C_{1-6}alkanediyl;

Z^c is a bivalent radical of formula -O-, -S- or -NR^3-;

R^{7c} is phenyl; phenyl substituted with 1 or 2 substituents selected from halo, C_{1-6}alkyl or C_{1-6}alkyloxy; furanyl; furanyl substituted with 1 or 2 substituents selected from C_{1-6}alkyl or hydroxyC_{1-6}alkyl; thienyl; thienyl substituted with 1 or 2 substituents selected from halo or C_{1-6}alkyl; oxazolyl; oxazolyl substituted with 1 or 2 C_{1-6}alkyl substituents; thiazolyl; thiazolyl substituted with 1 or 2 C_{1-6}alkyl substituents; pyridinyl or pyridinyl substituted with 1 or 2 C_{1-6}alkyl substituents;

R^{8c} is C_{1-6}alkyl or C_{1-6}alkyl substituted with hydroxy, carboxyl or C_{1-6}alkyloxycarbonyl;

R^{5c} is hydrogen, halo, hydroxy or C_{1-6}alkyloxy;

R^{6c} is hydrogen, C_{1-6}alkyl or Ar^1C_{1-6}alkyl;

each $-A^d-B^d-$ independently is a bivalent radical of formula

$-Y^d-CR^{7d}=CH-$ (D-b-1);

$-CH=CR^{7d}-Y^d-$ (D-b-2);

$-CH=CH-CH=CH-$ (D-b-3);

$-CH=CR^{7d}-CH=CH-$ (D-b-4);

$-CH=CH-CR^{7d}=CH-$ (D-b-5); or

$-CH=CH-CH=CR^{7d}-$ (D-b-6);

wherein each Y^d independently is a bivalent radical of formula -O-, -S- or $-NR^{8d}-$;

each R^{7d} independently is C_{1-6}alkyl; halo; ethenyl substituted with carboxyl or C_{1-6}alkyloxycarbonyl; hydroxyC_{1-6}alkyl; formyl; carboxyl or hydroxycarbonylC_{1-6}alkyl;

R^{8d} is hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl;

each Z^d independently is Z^{1d} or Z^{2d};

wherein Z^{1d} is a bivalent radical of formula $-CH_2-$, $-CH_2-CH_2-$ or -CH=CH-; provided that when L is a radical of formula (D-1) and the dotted line is an extra bond, then Z^{1d} is other than $-CH_2-$;

Z^{2d} is a bivalent radical of formula $-CH_2-CHOH-$, $-CH_2-O-$, $-CH_2-C(=O)-$ or $-CH_2-C(=NOH)-$, provided that the $-CH_2-$ moiety of said bivalent radicals is connected to the nitrogen of the imidazole ring;

each R^{4d} independently is hydrogen; C_{1-6}alkyl; halo; ethenyl substituted with carboxyl or C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with carboxyl or C_{1-6}alkyloxycarbonyl; hydroxyC_{1-6}alkyl; formyl or carboxyl;

each R^{5d} independently is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, Ar^1 or halo; or

R^{4d} and R^{5d} taken together may form a bivalent radical of formula -CH=CH-CH=CH- or $-CH_2-CH_2-CH_2-CH_2$;

each R^{6d} is hydrogen, C_{1-6}alkyl or Ar^1C_{1-6}alkyl.

Particular compounds are those compounds of formula (I) wherein R^1 is phenylmethyl; R^2 is phenyl substituted with 2 substituents selected from methyl or trifluoromethyl; n and m are 1; X is a covalent bond; and =Q is =O.

Also particular compounds are those compounds of formula (I) wherein L is a radical of formula (A), and suitably L^a is a radical of formula (a-2) wherein R^{4a} is hydrogen or phenyl; r is 0 or 1; Y^{1a} is a covalent bond, -O- or -NH-; R^{7a} is pyrrolidinyl, furanyl, 1-phenylcyclohexanyl, diphenylmethyl, or phenyl substituted with 1, 2 or 3 substituents each independently selected from methyl, methoxy or chloro.

Another particular group of compounds consists of those compounds of formula (I) wherein L is a radical of formula (B) wherein p is 1; R^{4b} is hydrogen; C_{1-4}alkyloxy-C_{1-4}alkyl, phenyl or phenyl substituted with halo; R^{5b} is phenyl; amino substituted with phenyl or substituted imidazolyl; or phenyl substituted with halo; or R^{5b} is a radical of formula (B-a-1) wherein Y^b is Y^{1b} or Y^{2b} wherein Y^{1b} is a covalent bond, -NR^{7b}- or -CH_2-NR^{7b}-; wherein R^{7b} is hydrogen or phenyl optionally substituted with halo; Y^{2b} is -O-; R^{9b} is C_{1-6}alkyl, C_{1-6}alkyloxy, pyrrolidinyl, phenylC_{1-6}alkyl, imidazolyl substituted with phenylC_{1-6}alkyl or Ar^{3b}; or R^{5b} is a radical of formula (B-a-2) wherein R^{10b} is hydrogen or C_{1-6}alkylcarbonyl; R^{11b} is hydrogen; or R^{4b} and R^{5b} are taken together to form a bivalent radical of formula -C(=O)-NR^3-CH_2-NR^{7b}- wherein each R^{7b} independently is selected from hydrogen or phenyl; and R^{6b} is hydrogen.

Another particular group of compounds consists of those compounds of formula (I) wherein L is a radical of formula (C-1) or (C-2) wherein ⋯Y^c— is -NH- or -O-; -A^c=B^c- is -CH=CH- or -N=CH-; R^{4c} is a radical of formula (C-c-1) wherein R^{7c} is oxazolyl substituted with 1 or 2 C_{1-6}alkyl substituents, furanyl substituted with C_{1-6}alkyl or hydroxyC_{1-6}alkyl; or R^{4c} is a radical of formula (C-c-2) wherein Z^c is a bivalent radical of formula -O-, and R^{8c} is C_{1-6}alkyl; R^{5c} is hydrogen; and R^{6c} is hydrogen.

Another particular group of compounds consists of those compounds of formula (I) wherein L is a radical of formula (D-1) wherein the dotted line is an optional bond; -A^d-B^d- is a radical of formula (D-b-1) wherein Y^d is -S-; and R^{7d} is hydrogen; or -A^d-B^d- is a radical of formula (D-b-2) wherein Y^d is -S- or -NR^{8d}-; and R^{7d} is hydrogen; or -A^d-B^d- is a radical of formula (D-b-3); Z^d is Z^{1d} or Z^{2d} wherein Z^{1d} is a bivalent radical of formula -CH_2- or -CH_2-CH_2-, provided that when the dotted line is an extra bond, then Z^{1d} is other than -CH_2-; and Z^{2d} is a bivalent radical of formula -CH_2-O-, -CH_2CHOH- or CH_2-C(=O)-, provided that the -CH_2- moiety of said bivalent radicals is connected to the nitrogen of the imidazole ring; R^{4d} is hydrogen, formyl or hydroxymethyl; R^{5d} is hydrogen; or R^{4d} and R^{5d} taken together form a bivalent radical of formula -CH=CH-CH=CH-; R^{6d} is hydrogen.

Yet another particular group of compounds consists of those compounds of formula (I) wherein L is a radical of formula (D-2) wherein -A^d-B^d- is a radical of formula (D-b-3); Z^d is a bivalent radical of formula -CH_2-CH_2-; R^{4d}, R^{5d} and R^{6d} are hydrogen.

Most preferred are those compounds selected from
1-[3,5-bis(trifluoromethyl)benzoyl]-4-[[1-(2-ethoxyethyl)-1*H*-benzimidazol-2-yl]-amino]-2-(phenylmethyl)piperidine;
1-[1,3-bis(trifluoromethyl)benzoyl]-4-[4-[[1-(2-ethoxyethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]-2-(phenylmethyl)piperidine;
1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-(2,3-dihydro-2-oxo-1*H*-benzimidazol-1-yl)-1-piperidinyl]-2-(phenylmethyl)piperidine;
1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-[4-phenyl-4-(1-pyrrolidinyl-carbonyl)-1-piperidinyl]piperidine;
N-[[1-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-4-phenyl-4-piperidinyl]methyl]acetamide;
1-[3,5-bis(trifluoromethyl)benzoyl]-4-[[1-[(2-methyl-4-oxazolyl)methyl]-1*H*-benz-imidazol-2-yl]amino]-2-(phenylmethyl)piperidine;
1-[3,5-bis(trifluoromethyl)benzoyl]-4-[[1-[(5-methyl-2-furanyl)methyl]-1*H*-benz-imidazol-2-yl]amino]-2-(phenylmethyl)piperidine;
1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-8-yl]-2-(phenylmethyl)piperidine;
4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide;
1-[3,5-bis(trifluoromethyl)benzoyl]-4-(5,6-dihydrospiro[11*H*-imidazo[2,1-b][3]-benzazepine-11,4'-piperidin]-1-yl)-2-(phenylmethyl)piperidine;
1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-[4-[a-(1-pyrrolidinylcarbonyl)-benzyl]-1-piperazinyl]piperidine;
1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-[[1-[(2-methyl-5-oxazolyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]-2-(phenylmethyl)piperidine;
1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-(5,6,9,10-tetrahydro-imidazo[1,2-a]thieno-[2,3-d]azepin-10-ylidene)-1-piperidinyl]-2-(phenylmethyl)piperidine;
1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-[[3-(5-methyl-2-furanyl)-3*H*-imidazo[4,5-b]-pyridin-2-yl]amino]-1-piperidinyl]-2-(phenylmethyl)piperidine;
1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-(5,6,7,10-tetrahydro-7-methylimidazo-[1,2-a]pyrrolo[3,2-d]azepin-10-ylidene)-1-piperidinyl]-2-(phenylmethyl)piperidine;
1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-(3-formyl-5,6-dihydro-11*H*-imidazo-[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]-2-(phenylmethyl)piperidine;

4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(1-phenylcyclohexyl)-1-piperazine acetamide;
1-[3,5-bis(trifluoromethyl)benzoyl]-4-[3-[[3-[(5-methyl-2-furanyl)methyl]-3*H*-imidazo-[4,5-b]pyridin-2-yl]amino]-1-pyrrolidinyl]-2-(phenylmethyl)piperidine;
1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-[[1-[(5-methyl-2-furanyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]piperidine;
1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(3,4-difluorophenyl)methyl]-4-[4-phenyl-4-(1-pyrrolidinylcarbonyl)-1-piperidinyl]piperidine;
4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide;
1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-[1-[(2-methyl-5-oxazolyl)methyl]-1*H*-benzimidazol-2-yl]-1-piperazinyl]-2-(phenylmethyl)piperidine;
4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(4-trifluoromethylphenyl)methyl]-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide;
1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-phenyl-4-(1-pyrrolidinylcarbonyl)-1-piperidinyl]-2-[[4-(trifluoromethyl)phenyl]methyl]piperidine;
4-[4-(5,6,7,10-tetrahydro-7-methylimidazo[1,2-a]pyrrolo[3,2-d]azepin-10-ylidene)-1-piperidinyl]-1-(3,5-dimethylbenzoyl)-2-(phenylmethyl)piperidine; and
4-[4-(5,6-dihydro-6-oxo-10*H*-imidazo[1,2-a]thieno[3,2-d]azepin-10-ylidene)-1-piperidinyl]-1-(3,5-dimethylbenzoyl)-2-(phenylmethyl)piperidine; the *N*-oxides, the stereoisomeric forms and the pharmaceutically acceptable addition salts thereof.

The compounds of formula (I) may be used alone or in conjunction with other agents which are known to beneficially influence the circadian timing system or to enhance sleep efficiency. The present compounds and the other agent may be coadministered, either in concomitant therapy or in a fixed combination, or they may be administered at separate times. For example, the present compounds may be administered in conjunction with other compounds which are known in the art to be useful for suppressing or stimulating melatonin production including melatonergic agents, noradrenergic and serotonergic re-uptake blockers, α_1-noradrenergic agonists, monamine oxidase inhibitors, neuropeptide Y agonists or antagonists; neurokinin- 1 agonists; substance P; beta-adrenergic blockers and benzodiazepines, such as atenolol; or with other compounds which are known in the art to be useful for stimulating melatonin production including tricyclic antidepressants and alpha-2-adrenergic antagonists; or with melatonin precursors such as tryptophan, 5-hydroxytryptophan, serotonin and N-acetylserotonin; as well as melatonin analogs, melatonin agonists and melatonin antagonists, or melatonin itself. In addition, the present compounds may be

administered in conjunction with other compounds which are known in the art to be useful for enhancing sleep quality and preventing and treating sleep disorders and sleep disturbances, including e.g., sedatives, hypnotics, anxiolytics, antipsychotics, anti-anxiety agents, minor tranquilizers, melatonin agonists and antagonists, melatonin, melatonergic agents, benzodiazepines, barbituates, $5HT_2$ antagonists, and the like, such as : adinazolam, allobarbital, alonimid, alprazolam, amitriptyline, amobarbital, amoxapine, bentazepam, benzoctamine, brotizolam, bupropion, busprione, butabarbital, butalbital, capuride, carbocloral, chloral betaine, chloral hydrate, chlordiazepoxide, clomipramine, cloperidone, clorazepate, clorethate, clozapine, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, estazolam, ethchlorvynol, etomidate, fenobam, flunitrazepam, flurazepam, fluvoxamine, fluoxetine, fosazepam, glutethimide, halazepam, hydroxyzine, imipramine, lithium, lorazepam, lometazepam, maprotiline, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, midaflur, midazolam, nefazodone, nisobamate, nitrazepam, nortriptyline, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, reclazepam, roletamide, secobarbital, sertraline, suproclone, temazepam, thioridazine, tracazolate, tranylcypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, valproate, venlafaxine, zaleplon, zolazepam, zolpidem, and salts thereof, and combinations thereof, and the like.

The present compounds may be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation. In particular, the present compounds may be administered in conjunction with scheduling bright light administration, ordinary-intensity light exposure, or exposure to dim-light or darkness (or even sleep).

Conveniently, a compound of the present invention is administered accompanied by having an individual wear dark or red goggles at the time of administration to provide additive effects of the treatment plus darkness. The contrary may also be beneficial, the individual wears dark goggles at times other than the time of administering a compound of the present invention. Similarly, bright light exposure can be used in conjunction with administration.

Accordingly, the present invention further includes within its scope the use of a compound of formula (I), alone or in combination with other agents, for beneficially

influencing the circadian timing system or enhance the sleep efficiency of a mammal, suitably a human being.

It will be appreciated to those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of the noted diseases/disorders and symptoms.

The present method of using one of the present compounds further provides an increase in the value which is calculated from the time that a subject sleeps divided by the time that a subject is attempting to sleep; a decrease in sleep latency (the time it takes to fall asleep); a decrease in the number of awakenings during sleep; a decrease in the time spent awake following the initial onset of sleep; an increase in the total amount of sleep; an increase in the amount and percentage of REM sleep; an increase in the duration and occurrence of REM sleep; a reduction in the fragmentation of REM sleep; an increase in the amount and percentage of slow-wave (i.e. stage 3 or 4) sleep; an increase in the amount and percentage of stage 2 sleep; a decrease in the number of awakenings, especially in the early morning; an increase in daytime alertness; and increased sleep maintenance; enhanced cognitive function; and increased memory retention.

The present invention is further useful for the prevention and treatment of sleep disorders and sleep disturbances including sleep problems associated with insomnia, hypersomnia, sleep apnea, narcolepsy, nocturnal myoclonus, REM sleep interruptions, jet-lag, shift workers' sleep disturbances, dysomnias, night terror, insomnias associated with depression or with emotional/mood disorders, as well as sleep walking and enuresis, as well as sleep disorders which accompany aging, conditions associated with circadian rhythmicity, mental and physical disorders associated with travel across time zones and with rotating shiftwork schedules, or syndromes such as fibromyalgia which are manifested by non-restorative sleep and muscle pain or sleep apnea which is associated with respiratory disturbances during sleep.

In addition, the present invention includes within its scope a pharmaceutical composition for beneficially influencing the circadian timing system or enhancing and improving the quality of sleep comprising, as an active ingredient, at least one of the compounds of the present invention in association with a pharmaceutical carrier or diluent.

It will be known to those skilled in the art that there are numerous compounds now being used to affect circadian rhythms or to enhance and improve the quality of sleep. Combinations of these therapeutic agents some of which have also been mentioned herein with a compound of the present invention will bring additional, complementary, and often synergistic properties to enhance the desirable properties of these various therapeutic agents.

The compounds of the present invention may be administered in combination with sedatives, hypnotics, anxiolytics, antipsychotics, antianxiety agents, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents, benzodiazepines, barbituates, $5HT_2$ antagonists, and the like, or present compounds may be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation. For example, to alter the circadian timing system or to enhance and improve the quality of sleep a compound of the present invention may be given in combination with adinazolam, allobarbital, alonimid, alprazolam, amitriptyline, amobarbital, amoxapine, bentazepam, benzoctamine, brotizolam, bupropion, busprione, butabarbital, butalbital, capuride, carbocloral, chloral betaine, chloral hydrate, chlordiazepoxide, clomipramine, cloperidone, clorazepate, clorethate, clozapine, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, estazolam, ethchlorvynol, etomidate, fenobam, flunitrazepam, flurazepam, fluvoxamine, fluoxetine, fosazepam, glutethimide, halazepam, hydroxyzine, imipramine, lithium, lorazepam, lormetazepam, maprotiline, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, midaflur, midazolam, nefazodone, nisobamate, nitrazepam, nortriptyline, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, reclazepam, roletamide, secobarbital, sertraline, suproclone, temazepam, thioridazine, tracazolate, tranylcypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, valproate, venlafaxine, zaleplon, zolazepam, zolpidem, and salts thereof, and combinations thereof, and the like, as well as admixtures and combinations thereof.

The dose ranges in which the present compounds may be administered alone or in combination with other therapeutic agents may be adjusted on a unit basis as necessary to permit divided daily dosage and, the dose will vary depending on the nature and severity of the disease, weight of patient, special diets and other factors.

These combinations may be formulated into pharmaceutical compositions as known in the art. For instance, a compound of the present invention may be administered alone or in combination by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual, or topical routes of administration and can be formulated in dosage forms appropriate for each route of administration.

The dosage of active ingredient in the compositions of this invention may be varied, however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The active ingredient may be administered to patients (animals and human) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. As will be readily apparent to one skilled in the art, the effect of a compound of the present invention which induces a phase shift in a central circadian pacemaker may be dependent on both the ambient and circadian time of administration. The same compound may induce a phase advance, a phase delay or have minor effect on a particular circadian rhythm depending on the circadian time of administration. The dose will vary from patient to patient depending upon the nature and severity of disease, the patient's weight, special diets then being followed by a patient, concurrent medication, the intrinsic tachykinin antagonist activity of the compound, the bioavailability upon oral administration of the compound and other factors which those skilled in the art will recognize.

Experimental part

For the purpose of the following experiments, male Syrian hamsters (*Mesocricetus auratus*) were purchased from Charles-River Lak:LVG (Saint-Aubin-lès-Elbeuf, F) and remained under 14 h light – 10 h dark cycle for two weeks prior to the start of each experiment. During daytime, light intensity was about 100 lux at the level of the cages. All animals were individually housed with access to a running wheel (diameter: 17 cm) for the continuous recording of wheel-running activity using the Chronobiology Kit (Stanford Software Systems, Stanford, CA).

Values produced by the following experiments are means ± SEM. Analyses of variance (ANOVA) with repeated measures followed by a Student-Newman-Keuls test were performed.

Compound 1 has been tested as described hereinafter and corresponds to (2R-trans)-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-N-(2,6-dimethylphenyl)-1-acetamide (S) hydroxybutanedioate (1:1).

Experiment 1: Injections of compound 1 before a light pulse in hamsters kept in constant darkness

Experiment 1 was designed to investigate the reducing effects of compound 1 on the light-induced phase-shifts.

(1) First, a dose response curve was generated for the possible effects of the injection of compound 1 on the light-induced phase-advances. Twenty-four hamsters were housed in constant darkness. After at least 10 days, half the animals received a single i.p. injection of 1.25 mg/kg, 2.5 mg/kg, 5.0 mg/kg or 10 mg/kg of compound 1 in 0.5 ml of vehicle. The other half received 0.5 ml of vehicle. Thirty minutes after the treatment, hamsters were exposed to a light pulse at circadian time (CT) 19 (i.e., 7 h after the time of activity onset, designated as CT12), a time when light produces large phase-advances. For light stimulation, hamsters were individually exposed to 100 lx of fluorescent white light for 10 minutes. The experiment was then repeated after 10 days, using a cross-over design in which the animals received the alternate treatment. (2) Thereafter, the effects of a single i.p. injection of compound 1 (5 mg/kg) on the phase-delaying and phase-advancing effects of a light pulse were determined. For that purpose, sixteen hamsters were housed in constant darkness. A first group of eight animals was injected two times with vehicle or compound 1. Thirty minutes after the treatment, hamsters were exposed to a light pulse at CT14, a time when light produces large phase-delays in the circadian activity rhythm of hamsters. No animal received the same treatment more than once. The order of injections was determined randomly. A second group of eight hamsters was injected similarly 30 minutes before being exposed to a light pulse at CT19.

Results are depicted in figures 1 and 2.

Figure 1 : Dose-dependence of compound 1-induced reduction of photic phase advances. Each animal was kept in constant darkness and treated with vehicle and compound 1 30 min before being exposed to a light pulse (100 lux for 10 min) at CT19. Data are means ± SEM (n = 6 per group). Groups with no letters in common differ significantly from one another ($P < 0.05$).

Figure 2 : Light-induced phase-shifts in circadian activity rhythms of hamsters pre-treated with compound 1. Positive and negative values are advances and delays,

respectively. Values are means ± SEM (n = 7 per group). Groups with no letters in common differ significantly from one another ($P < 0.05$).

Figures 1 and 2 show that when hamsters were treated with compound 1 before being exposed to a light pulse at CT19, the subsequent light-induced phase-advances were significantly reduced. There was a significant effect of the dose of compound ($P < 0.05$; see Figure 1). Compound 1 (5 mg/kg) reduced the light-induced phase-advances by 36 % ($P < 0.01$; see Figure 2). A light pulse applied at CT14 resulted in phase-delays of the free-running rhythm of locomotor activity (see Figure 2). The magnitude of the light-induced phase-delays was not affected by injections of compound 1 compared to those of vehicle (-54.4 ± 4.6, vs. -45.4 ± 4.6 min; $P > 0.05$; see Figure 2). There were no significant changes in the circadian period before vs. after the treatment at CT14 or CT19.

Experiment 2: Injections of compound 1 <u>after</u> a light pulse in hamsters kept in constant darkness

In experiment 2, the effects were investigated of a single i.p. injection of compound 1 (5 mg/kg) on the phase-advancing effects of light pulses when the drug was administered after animals were exposed to a 10-min light pulse at CT19. This treatment was done on two occasions in six animals kept in constant darkness who were randomly injected with vehicle or compound 1. No animal received the same treatment more than once.

Results are depicted in figure 3.

Figure 3 : Light-induced phase-advances in circadian activity rhythms of hamsters treated with compound 1, after exposure to light. Values are means ± SEM (n = 6 per group). No significant difference was detectable between the groups ($P > 0.05$).

Light-induced phase-advances were not significantly altered when hamsters were treated with compound 1 (5 mg/kg) after being exposed to a light pulse at CT19 in comparison with vehicle treatment (104.2 ± 14.4 vs. 114.7 ± 14.3 min, respectively; $P > 0.05$; see Figure 3). The circadian period was not significantly affected by the treatment. This result indicates that modulation of the light-induced phase-advances by compound 1 is no longer detectable when this substance P antagonist is injected after the light pulse. This demonstrates that the compounds of the present invention can be used in the manufacture of a medicament useful for anticipating or preventing circadian rhythm disturbances caused by light exposure at an inappropriate circadian time. In

addition, because the induction of genes involved in the molecular regulation of photic phase resetting is very quick (<20 min; e.g., Ginty et al., 1993, Science 260, 238-241; Shigeyoshi et al., 1997, Cell 91, 1043-1053), this finding suggests that substance P modulates transmission of photic information before it reaches the core of the SCN circadian oscillator (i.e., at the retina and/or the retino-hypothalamic terminals).

Experiment 3: Injections of compound 1 in hamsters kept in constant light

Experiment 3 was designed to test the ability of compound 1 to mimic the effects of dark pulses in animals kept in constant light. Dark pulses typically induce phase-advances and phase-delays in circadian rhythm of locomotor activity when applied, respectively, during the mid-subjective day and the late subjective night (Boulos and Rusak, 1982, J. Comp. Physiol. A 146, 411-417; Ellis et al., 1982, Am. J. Physiol. 242, R44-R50; Van Reeth and Turek, 1989, . Nature 339, 49-51). Therefore, sixteen hamsters were kept in constant light (100 lux). A first group of eight animals was injected two times with vehicle or compound 1 at CT8. No animal received the same treatment more than once. The order of injections was determined randomly. A second group of eight hamsters was similarly treated with injections occurring at CT19.

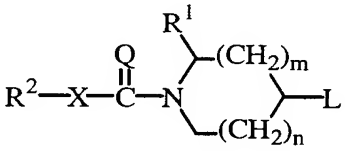
Results are depicted in figure 4.

Figure 4 : Phase-advances in circadian activity rhythms of hamsters housed in constant light. Animals were treated with vehicle and compound 1 (5 mg/kg) at CT8 or CT19. Values are means ± SEM ($n = 7$ per group). Groups with no letters in common differ significantly from one another ($P < 0.05$).

Figure 4 shows that injection of compound 1 (5 mg/kg) at CT8 led to phase-advances in the circadian rhythm of activity in hamsters compared to vehicle injections (39.5 ± 7.5 vs. 9.5 ± 3.6 min; $P < 0.05$). Injections of compound 1 (5 mg/kg) or vehicle at CT19 had no phase-shifting effects (7.5 ± 5.2 and 1.6 ± 3.9 min respectively). The circadian period was not significantly affected by the injections of compound 1 or vehicle.

Claims

1. The use of a compound of formula (I) for the preparation of a medicament useful for beneficially influencing the circadian timing system of a mammal wherein the compound of formula (I) is



(I)

a *N*-oxide form, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein

n is 0, 1 or 2;

m is 1 or 2, provided that if m is 2, then n is 1;

=Q is =O or =NR^3;

X is a covalent bond or a bivalent radical of formula -O-, -S-, -NR^3-;

R^1 is Ar^1, Ar^1C_{1-6}alkyl or di(Ar^1)C_{1-6}alkyl, wherein each C_{1-6}alkyl group is optionally substituted with hydroxy, C_{1-4}alkyloxy, oxo or a ketalized oxo substituent of formula -O-CH_2-CH_2-O- or -O-CH_2-CH_2-CH_2-O-;

R^2 is Ar^2, Ar^2C_{1-6}alkyl, Het^1 or Het^1C_{1-6}alkyl;

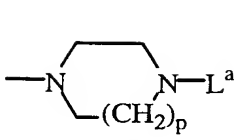
each R^3 independently is hydrogen or C_{1-6}alkyl;

each Ar^1 independently is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-4}alkyl, haloC_{1-4}alkyl, cyano, aminocarbonyl, C_{1-4}alkyloxy or haloC_{1-4}alkyloxy;

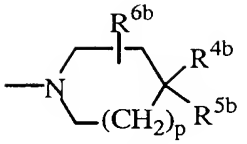
Ar^2 is naphtalenyl; phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from hydroxy, halo, cyano, nitro, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkyloxy, haloC_{1-4}alkyloxy, carboxyl, C_{1-4}alkyloxycarbonyl, aminocarbonyl and mono- or di(C_{1-4}alkyl)aminocarbonyl;

Het^1 is a monocyclic heterocycle selected from pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl and benzothienyl; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom by 1 or 2 substituents selected from halo, C_{1-4}alkyl or mono-, di- or tri(halo)methyl;

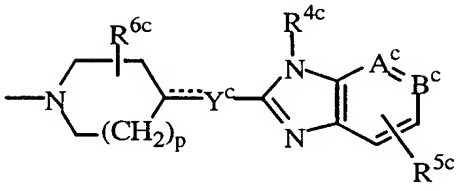
L is a radical of formula



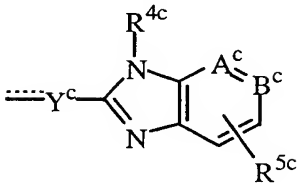
(A)



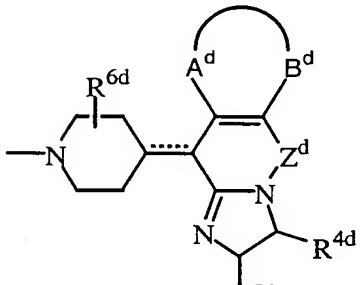
(B)



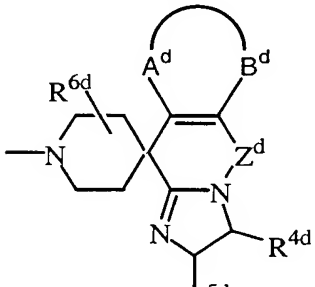
(C-1)



(C-2)



(D-1)

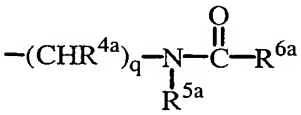


(D-2)

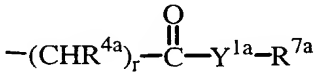
wherein

each p independently is 1 or 2;

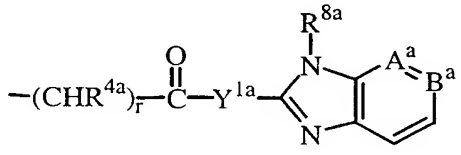
L^a is hydrogen; Ar^{3a}; C_{1-6}alkyl; C_{1-6}alkyl substituted with 1 or 2 substituents selected from hydroxy, C_{1-6}alkyloxy, Ar^{3a}, $Ar^{3a}C_{1-6}$alkyloxy and Het^{2a}; C_{3-6}alkenyl; $Ar^{3a}C_{3-6}$alkenyl; di(Ar^{3a})C_{3-6}alkenyl or a radical of formula



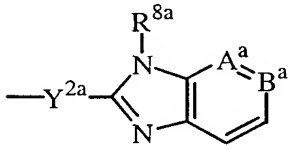
(A-a-1)



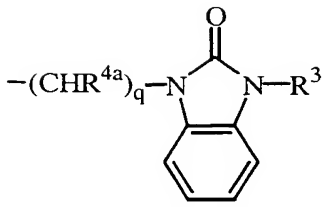
(A-a-2)



(A-a-3)



(A-a-4); or



(A-a-5)

wherein each q independently is 2, 3 or 4;

each r independently is 0, 1, 2, 3 or 4;

each Y^{1a} independently is a covalent bond, -O- or NR^3;

Y^{2a} is a covalent bond, C_{1-4}alkanediyl or -C_{1-4}alkylNR^3-;

each -A^a=B^a- independently is a bivalent radical of formula -CH=CH-, -N=CH- or -CH=N-;

each R^{4a} independently is hydrogen, C_{1-6}alkyl, Ar^2 or Ar^2C_{1-6}alkyl;

R^{5a} is hydrogen, C_{1-6}alkyl or Ar^{3a};

R^{6a} is C_{1-6}alkyl, Ar^{3a}, $Ar^{3a}C_{1-6}$alkyl, di(Ar^{3a})C_{1-6}alkyl, $Ar^{3a}C_{3-7}$cycloalkyl, or indolyl;

R^{7a} is Ar^{3a}; $Ar^{3a}C_{1-6}$alkyl; di(Ar^{3a})C_{1-6}alkyl; C_{1-6}alkyl; C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with Ar^{3a}; oxazolyl; oxazolyl substituted with halo or C_{1-6}alkyl; thiazolyl; thiazolyl substituted with halo or C_{1-6}alkyl; imidazolyl; imidazolyl substituted with Ar^{3a}, C_{1-6}alkyl, $Ar^{3a}C_{1-6}$alkyl or halo; indolinyl; indolinyl substituted with C_{1-4}alkyl; 2,3,4-trihydroquinolinyl; pyrrolidinyl or furanyl;

each R^{8a} independently is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl or a radical of formula

-Alk^a-R^{11a} (A-b-1) or

-Alk^a-Z^a-R^{12a} (A-b-2);

wherein Alk^a is C_{1-6}alkanediyl;

Z^a is a bivalent radical of formula -O-, -S- or -NR^3-;

R^{11a} is phenyl; phenyl substituted with 1 or 2 substituents selected from halo, C_{1-6}alkyl or C_{1-6}alkyloxy; furanyl; furanyl substituted with 1 or 2 substituents selected from C_{1-6}alkyl or hydroxy-C_{1-6}alkyl; thienyl; thienyl substituted with 1 or 2 substituents selected from halo or C_{1-6}alkyl; oxazolyl; oxazolyl substituted with 1 or 2 C_{1-6}alkyl substituents; thiazolyl; thiazolyl substituted with 1 or 2 C_{1-6}alkyl substituents; pyridinyl or pyridinyl substituted with 1 or 2 C_{1-6}alkyl substituents;

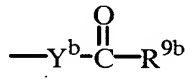
R^{12a} is C_{1-6}alkyl or C_{1-6}alkyl substituted with hydroxy, carboxyl or C_{1-6}alkyloxycarbonyl;

each Ar^{3a} independently is phenyl or phenyl substituted with 1, 2 or 3 substituents selected from halo, hydroxy, amino, nitro, aminocarbonyl, C_{1-6}alkyl, haloC_{1-6}alkyl or C_{1-6}alkyloxy;

each Het^{2a} independently is a heterocycle selected from 1,4-dihydro-5-oxo-tetrazol-1-yl, imidazo[1,2-a]pyridinyl, oxazolyl or imidazolyl; each of said heterocycles may be substituted with 1 or where possible 2 substituents selected from C_{1-4}alkyl and Ar^{3a};

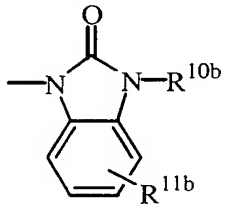
R^{4b} is hydrogen; C_{1-4}alkyl; C_{1-4}alkyloxyC_{1-4}alkyl; hydroxyC_{1-4}alkyl; carboxyl; C_{1-4}alkyloxycarbonyl or Ar^{3b};

R^{5b} is hydrogen; hydroxy; Ar^{3b}; $Ar^{3b}C_{1-6}$alkyloxy; di(Ar^{3b})C_{1-6}alkyloxy; $Ar^{3b}C_{1-6}$alkylthio; di(Ar^{3b})C_{1-6}alkylthio; $Ar^{3b}C_{1-6}$alkylsulfoxy; di(Ar^{3b})C_{1-6}alkylsulfoxy; $Ar^{3b}C_{1-6}$alkylsulfonyl; di(Ar^{3b})C_{1-6}alkylsulfonyl; $-NR^{7b}R^{8b}$; C_{1-6}alkyl substituted with $-NR^{7b}R^{8b}$; or a radical of formula



(B-a-1)

or



(B-a-2)

wherein R^{7b} is hydrogen; C_{1-6}alkyl; pyridinyl or Ar^{3b};

R^{8b} is hydrogen; C_{1-6}alkyl; $Ar^{3b}C_{1-6}$alkyl; di(Ar^{3b})C_{1-6}alkyl; imidazolyl substituted with Ar^{3b}, C_{1-6}alkyl or $Ar^{3b}C_{1-6}$alkyl; benzoxazolyl or benzothiazolyl;

R^{9b} is hydrogen; hydroxy; C_{1-6}alkyl; C_{1-6}alkyloxy; Ar^{3b}; $Ar^{3b}C_{1-6}$alkyl; di(Ar^{3b})-C_{1-6}alkyl; amino; mono- or di(C_{1-6}alkyl)amino; imidazolyl; imidazolyl substituted with Ar^{3b}, C_{1-6}alkyl or $Ar^{3b}C_{1-6}$alkyl; pyrrolidinyl; piperidinyl; homopiperidinyl; morpholinyl or thiomorpholinyl;

R^{10b} is hydrogen or C_{1-6}alkylcarbonyl;

R^{11b} is hydrogen; halo or mono-, di- or tri(halo)methyl;

Y^b is Y^{1b} or Y^{2b},

wherein Y^{1b} is a covalent bond; C_{1-6}alkanediyl; $-NR^{7b}-$ or $-C_{1-6}$alkanediyl-$NR^{7b}-$; or

Y^{2b} is -O-, provided that R^{9b} is other than hydroxy or C_{1-6}alkyloxy;

R^{4b} and R^{5b} may also be taken together to form a bivalent radical of formula $-O-CH_2-CH_2-O-$ or $-C(=O)-NR^3-CH_2-NR^{7b}-$;

R^{6b} is hydroxy; C_{1-6}alkyloxy; C_{1-6}alkyl or $Ar^{3b}C_{1-6}$alkyl;

Ar^{3b} is phenyl or phenyl substituted with 1, 2 or 3 substituents selected from halo, hydroxy, amino, nitro, aminocarbonyl, C_{1-6}alkyl, haloC_{1-6}alkyl or C_{1-6}alkyloxy;

$\overset{\cdots}{=}Y^c-$ is a bivalent radical of formula $-CH_2-$, -CH(OH)-, -C(=O)-, -O-, -S-, $-S(=O)_2-$, $-NR^3-$, $-CH_2-NR^3-$ or $-C(=O)-NR^3-$; or a trivalent radical of formula =CH-;

$-A^c=B^c-$ is a bivalent radical of formula -CH=CH-, -N=CH- or -CH=N-;

R^{4c} is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl or a radical of formula

$-Alk^c-R^{7c}$ (C-c-1) or

$-Alk^c-Z^c-R^{8c}$ (C-c-2);

wherein Alk^c is C_{1-6}alkanediyl;

Z^c is a bivalent radical of formula -O-, -S- or $-NR^3-$;

R^{7c} is phenyl; phenyl substituted with 1 or 2 substituents selected from halo, C_{1-6}alkyl or C_{1-6}alkyloxy; furanyl; furanyl substituted with 1 or 2 substituents selected from C_{1-6}alkyl or hydroxyC_{1-6}alkyl; thienyl substituted with 1 or 2 substituents selected from halo or C_{1-6}alkyl; oxazolyl; oxazolyl substituted with 1 or 2 C_{1-6}alkyl substituents; thiazolyl; thiazolyl substituted with 1 or 2 C_{1-6}alkyl substituents; pyridinyl or pyridinyl substituted with 1 or 2 C_{1-6}alkyl substituents;

R^{8c} is C_{1-6}alkyl or C_{1-6}alkyl substituted with hydroxy, carboxyl or C_{1-6}alkyloxycarbonyl;

R^{5c} is hydrogen, halo, hydroxy or C_{1-6}alkyloxy;

R^{6c} is hydrogen, C_{1-6}alkyl or Ar^1C_{1-6}alkyl;

each $-A^d-B^d-$ independently is a bivalent radical of formula

$-Y^d-CR^{7d}=CH-$ (D-b-1);

$-CH=CR^{7d}-Y^d-$ (D-b-2);

-CH=CH-CH=CH- (D-b-3);

$-CH=CR^{7d}-CH=CH-$ (D-b-4);

$-CH=CH-CR^{7d}=CH-$ (D-b-5); or

$-CH=CH-CH=CR^{7d}-$ (D-b-6);

wherein each Y^d independently is a bivalent radical of formula -O-, -S- or $-NR^{8d}-$;

each R^{7d} independently is C_{1-6}alkyl; halo; ethenyl substituted with carboxyl or C_{1-6}alkyloxycarbonyl; hydroxyC_{1-6}alkyl; formyl; carboxyl or hydroxycarbonylC_{1-6}alkyl;

R^{8d} is hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl;

each Z^d independently is Z^{1d} or Z^{2d};

wherein Z^{1d} is a bivalent radical of formula -CH_2-, -CH_2-CH_2- or -CH=CH-; provided that when L is a radical of formula (D-1) and the dotted line is an extra bond, then Z^{1d} is other than -CH_2-;

Z^{2d} is a bivalent radical of formula -CH_2-CHOH-, -CH_2-O-, -CH_2-C(=O)- or -CH_2-C(=NOH)-, provided that the -CH_2- moiety of said bivalent radicals is connected to the nitrogen of the imidazole ring;

each R^{4d} independently is hydrogen; C_{1-6}alkyl; halo; ethenyl substituted with carboxyl or C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with carboxyl or C_{1-6}alkyloxycarbonyl; hydroxyC_{1-6}alkyl; formyl or carboxyl;

each R^{5d} independently is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, Ar^1 or halo; or

R^{4d} and R^{5d} taken together may form a bivalent radical of formula -CH=CH-CH=CH- or -CH_2-CH_2-CH_2-CH_2;

each R^{6d} is hydrogen, C_{1-6}alkyl or Ar^1C_{1-6}alkyl.

2. The use of a compound of formula (I) as claimed in claim 1 wherein L is a radical of formula (A); r is 0 or 1; Y^{1a} is a covalent bond, -O- or -NH-; R^{7a} is pyrrolidinyl, furanyl, 1-phenylcyclohexanyl, diphenylmethyl, or phenyl substituted with 1, 2 or 3 substituents each independently selected from methyl, methoxy or chloro.

3. The use of a compound of formula (I) as claimed in claim 1 wherein L is a radical of formula (B) wherein p is 1; R^{4b} is hydrogen; C_{1-4}alkyloxyC_{1-4}alkyl, phenyl or phenyl substituted with halo; R^{5b} is phenyl, amino substituted with phenyl or substituted imidazolyl, or phenyl substituted with halo; or R^{5b} is a radical of formula (B-a-1) wherein Y^b is Y^{1b} or Y^{2b} wherein Y^{1b} is a covalent bond, -NR^{7b}- or -CH_2-NR^{7b}-; wherein R^{7b} is hydrogen or phenyl optionally substituted with halo; Y^{2b} is -O-; R^{9b} is C_{1-6}alkyl, C_{1-6}alkyloxy, pyrrolidinyl, phenylC_{1-6}alkyl, imidazolyl substituted with phenylC_{1-6}alkyl or Ar^{3b}; or R^{5b} is a radical of formula (B-a-2) wherein R^{10b} is hydrogen or C_{1-6}alkylcarbonyl; R^{11b} is hydrogen; or R^{4b} and R^{5b} are taken together to form a bivalent radical of formula -C(=O)-NR^3-CH_2-NR^{7b}- wherein each R^{7b} independently is selected from hydrogen or phenyl; and R^{6b} is hydrogen.

4. The use of a compound of formula (I) as claimed in claim 1 wherein L is a radical of formula (C-1) or (C-2) wherein $\cdots Y^c —$ is -NH- or -O-; -A^c=B^c- is -CH=CH- or -N=CH-; R^{4c} is a radical of formula (C-c-1) wherein R^{7c} is oxazolyl substituted with 1 or 2 C_{1-6}alkyl substituents, furanyl substituted with C_{1-6}alkyl or hydroxyC_{1-6}alkyl; or

R^{4c} is a radical of formula (C-c-2) wherein Z^c is a bivalent radical of formula -O-, and R^{8c} is C_{1-6}alkyl; R^{5c} is hydrogen; and R^{6c} is hydrogen.

5. The use of a compound of formula (I) as claimed in claim 1 wherein L is a radical of formula (D-1) wherein the dotted line is an optional bond; $-A^d-B^d-$ is a radical of formula (D-b-1) wherein Y^d is -S-; and R^{7d} is hydrogen; or $-A^d-B^d-$ is a radical of formula (D-b-2) wherein Y^d is -S- or $-NR^{8d}-$; and R^{7d} is hydrogen; or $-A^d-B^d-$ is a radical of formula (D-b-3); Z^d is Z^{1d} or Z^{2d} wherein Z^{1d} is a bivalent radical of formula $-CH_2-$ or $-CH_2-CH_2-$, provided that when the dotted line is an extra bond, then Z^{1d} is other than $-CH_2-$; and Z^{2d} is a bivalent radical of formula $-CH_2-O-$, $-CH_2CHOH-$ or $CH_2-C(=O)-$, provided that the $-CH_2-$ moiety of said bivalent radicals is connected to the nitrogen of the imidazole ring; R^{4d} is hydrogen, formyl or hydroxymethyl; R^{5d} is hydrogen; or R^{4d} and R^{5d} taken together form a bivalent radical of formula -CH=CH-CH=CH-; R^{6d} is hydrogen.

6. The use of a compound of formula (I) as claimed in claim 1 wherein L is a radical of formula (D-2) wherein $-A^d-B^d-$ is a radical of formula (D-b-3); Z^d is a bivalent radical of formula $-CH_2-CH_2-$; R^{4d}, R^{5d} and R^{6d} are hydrogen.

7. The use of a compound of formula (I) as claimed in claim 1 wherein the compound is

1-[3,5-bis(trifluoromethyl)benzoyl]-4-[[1-(2-ethoxyethyl)-1*H*-benzimidazol-2-yl]-amino]-2-(phenylmethyl)piperidine;

1-[1,3-bis(trifluoromethyl)benzoyl]-4-[4-[[1-(2-ethoxyethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]-2-(phenylmethyl)piperidine;

1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-(2,3-dihydro-2-oxo-1*H*-benzimidazol-1-yl)-1-piperidinyl]-2-(phenylmethyl)piperidine;

1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-[4-phenyl-4-(1-pyrrolidinyl-carbonyl)-1-piperidinyl]piperidine;

N-[[1-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-4-phenyl-4-piperidinyl]methyl]acetamide;

1-[3,5-bis(trifluoromethyl)benzoyl]-4-[[1-[(2-methyl-4-oxazolyl)methyl]-1*H*-benz-imidazol-2-yl]amino]-2-(phenylmethyl)piperidine;

1-[3,5-bis(trifluoromethyl)benzoyl]-4-[[1-[(5-methyl-2-furanyl)methyl]-1*H*-benz-imidazol-2-yl]amino]-2-(phenylmethyl)piperidine;

1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-8-yl]-2-(phenylmethyl)piperidine;

4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide;

1-[3,5-bis(trifluoromethyl)benzoyl]-4-(5,6-dihydrospiro[11*H*-imidazo[2,1-b][3]-benzazepine-11,4'-piperidin]-1-yl)-2-(phenylmethyl)piperidine;

1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-[4-[a-(1-pyrrolidinylcarbonyl)-benzyl]-1-piperazinyl]piperidine;

1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-[[1-[(2-methyl-5-oxazolyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]-2-(phenylmethyl)piperidine;

1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-(5,6,9,10-tetrahydro-imidazo[1,2-a]thieno-[2,3-d]azepin-10-ylidene)-1-piperidinyl]-2-(phenylmethyl)piperidine;

1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-[[3-(5-methyl-2-furanyl)-3*H*-imidazo[4,5-b]-pyridin-2-yl]amino]-1-piperidinyl]-2-(phenylmethyl)piperidine;

1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-(5,6,7,10-tetrahydro-7-methylimidazo-[1,2-a]pyrrolo[3,2-d]azepin-10-ylidene)-1-piperidinyl]-2-(phenylmethyl)piperidine;

1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-(3-formyl-5,6-dihydro-11*H*-imidazo-[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]-2-(phenylmethyl)piperidine;

4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(1-phenyl-cyclohexyl)-1-piperazine acetamide;

1-[3,5-bis(trifluoromethyl)benzoyl]-4-[3-[[3-[(5-methyl-2-furanyl)methyl]-3*H*-imidazo-[4,5-b]pyridin-2-yl]amino]-1-pyrrolidinyl]-2-(phenylmethyl)piperidine;

1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-[[1-[(5-methyl-2-furanyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]piperidine;

1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(3,4-difluorophenyl)methyl]-4-[4-phenyl-4-(1-pyrrolidinylcarbonyl)-1-piperidinyl]piperidine;

4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide;

1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-[1-[(2-methyl-5-oxazolyl)methyl]-1*H*-benzimidazol-2-yl]-1-piperazinyl]-2-(phenylmethyl)piperidine;

4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(4-trifluoromethylphenyl)methyl]-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide;

1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-phenyl-4-(1-pyrrolidinylcarbonyl)-1-piperidinyl]-2-[[4-(trifluoromethyl)phenyl]methyl]piperidine;

4-[4-(5,6,7,10-tetrahydro-7-methylimidazo[1,2-a]pyrrolo[3,2-d]azepin-10-ylidene)-1-piperidinyl]-1-(3,5-dimethylbenzoyl)-2-(phenylmethyl)piperidine; and

4-[4-(5,6-dihydro-6-oxo-10*H*-imidazo[1,2-a]thieno[3,2-d]azepin-10-ylidene)-1-piperidinyl]-1-(3,5-dimethylbenzoyl)-2-(phenylmethyl)piperidine;

a *N*-oxide, a stereoisomeric form or a pharmaceutically acceptable addition salt thereof.

8. The use of a compound of formula (I) as claimed in any one of claims 1 to 7 wherein beneficially influencing the circadian timing system is blocking or reducing the phase shifting effects of light.

9. The use of a compound of formula (I) as claimed in any one of claims 1 to 7 wherein beneficially influencing the circadian timing system is anticipating or preventing circadian rhythm disturbances caused by light exposure at an inappropriate circadian time.

10. The use of a compound of formula (I) as claimed in any one of claims 1 to 7 wherein beneficially influencing the circadian timing system achieving a chronobiologic effect and alleviating circadian rhythm disorders.

11. The use of a compound of formula (I) as claimed in any one of claims 1 to 7 wherein beneficially influencing the circadian timing system is enhancing or improving sleep quality.

12. The use of a compound of formula (I) as claimed in any one of claims 1 to 7 wherein beneficially influencing the circadian timing system is preventing and treating sleep disorders and sleep disturbances.

13. The use of a compound of formula (I) as claimed in any one of claims 1 to 11 wherein the mammal is a human being.

14. The use of a compound of formula (I) as claimed in any one of claims 1 to 12 in combination with other agents or therapies known to beneficially influence the circadian timing system.

Figure 1

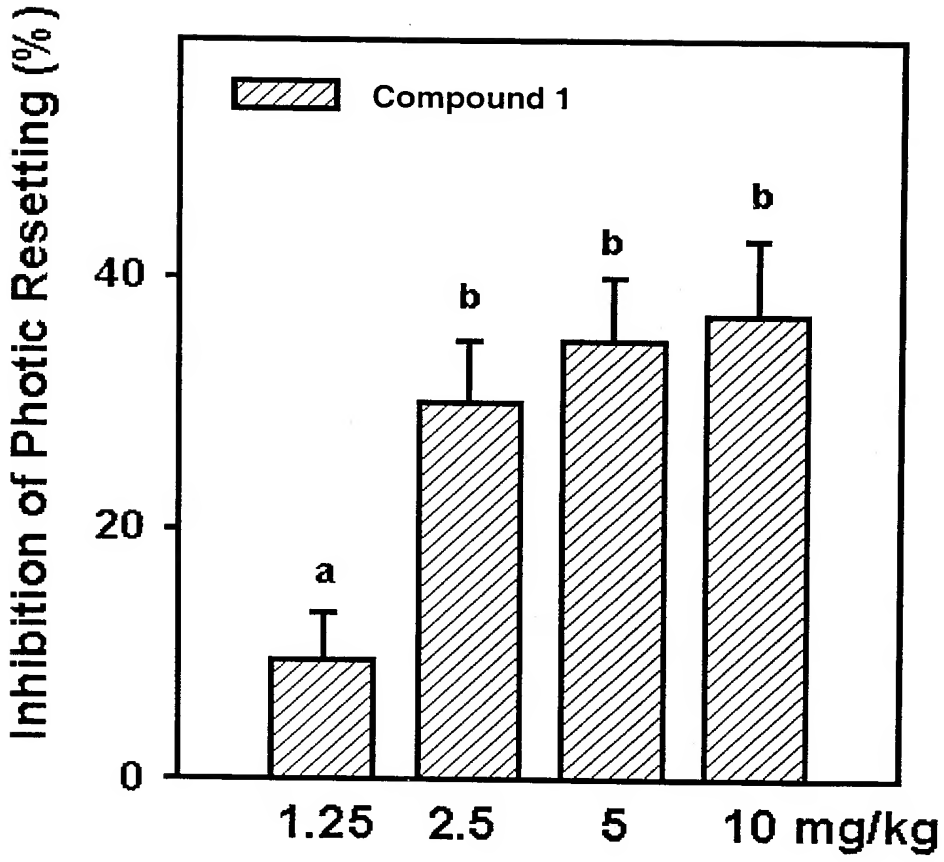

Inhibition of Photic Resetting (%)
Compound 1
0
20
40
a
b
b
b
1.25
2.5
5
10 mg/kg

Figure 2

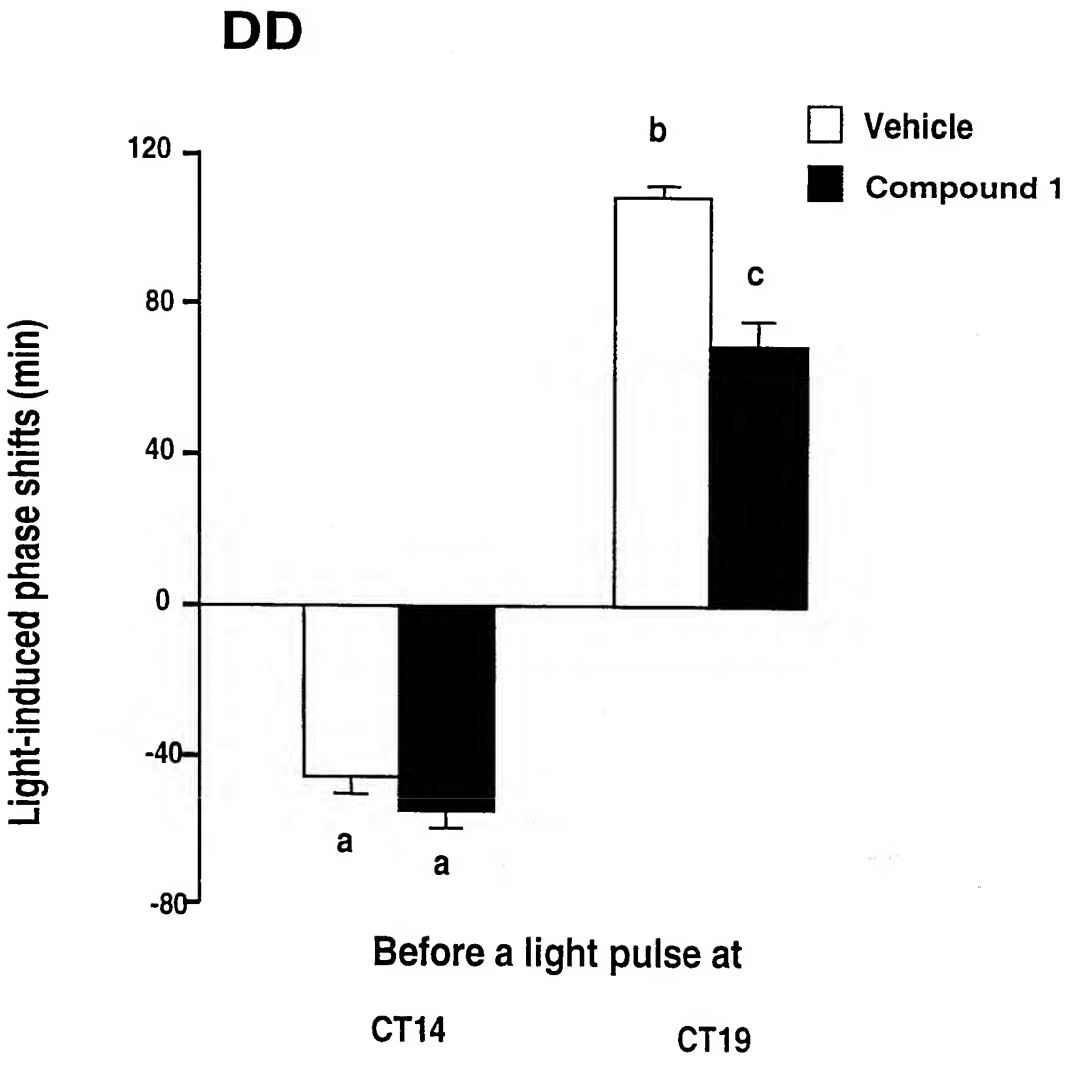

DD
Vehicle
Compound 1
b
c
a
a
120
80
40
0
-40
-80
Light-induced phase shifts (min)
Before a light pulse at
CT14
CT19

Figure 3

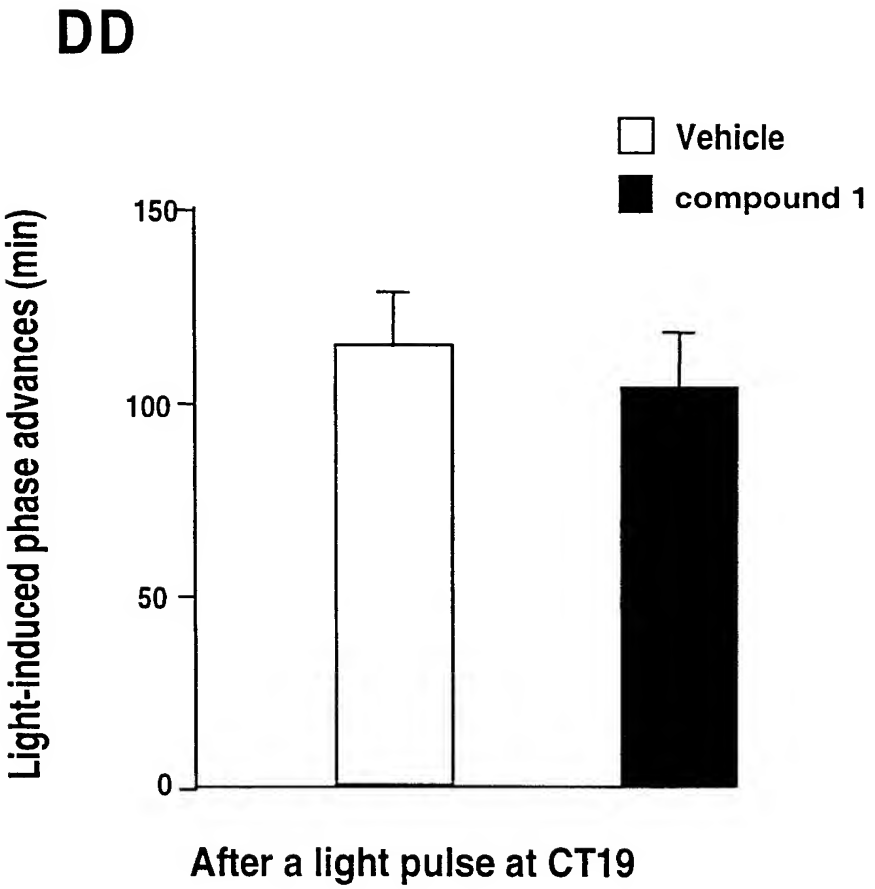
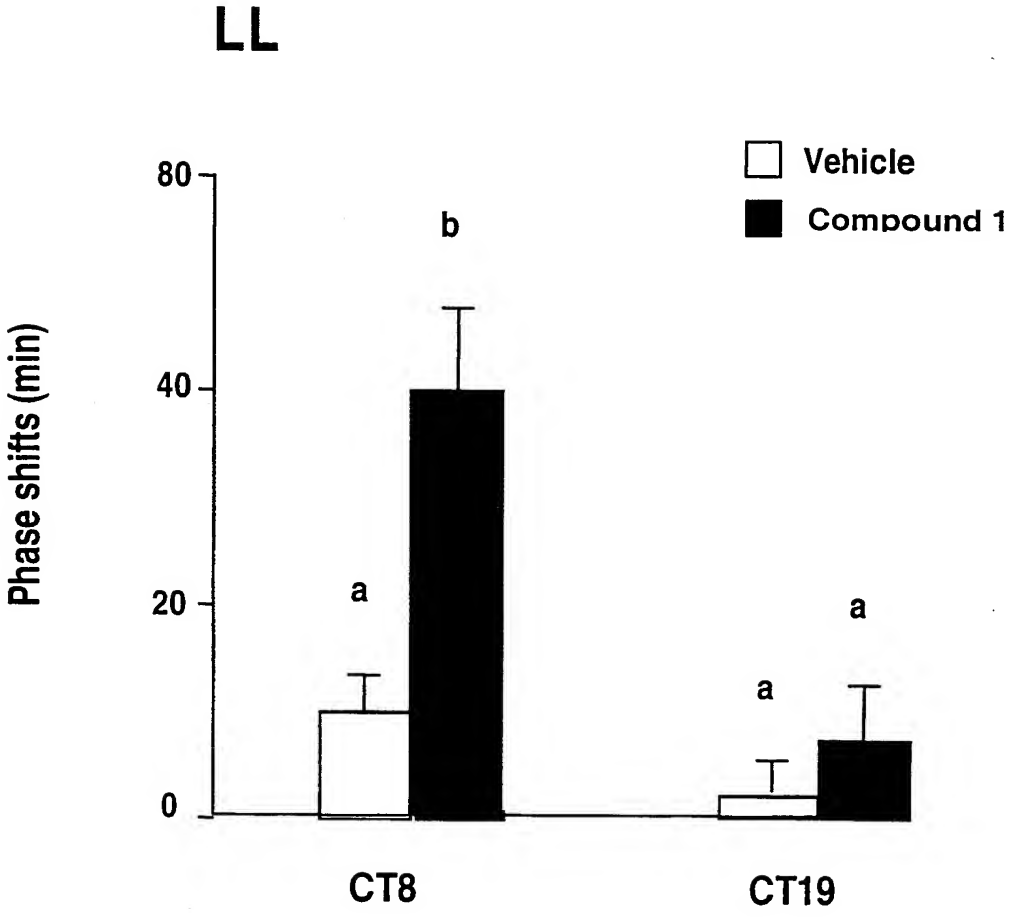

DD
Vehicle
compound 1
Light-induced phase advances (min)
150
100
50
0
After a light pulse at CT19

Figure 4


LL
Vehicle
Compound 1
Phase shifts (min)
80
40
20
0
a
b
a
a
CT8
CT19

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/EP 00/10201

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 16440 A (JANSSEN PHARMACEUTICA NV ;JANSSENS FRANS EDUARD (BE); SOMMEN FRANC) 9 May 1997 (1997-05-09) cited in the application the whole document ---	1-14
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 January 2001	19/01/2001

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Interr nal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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